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Preparation of hydrogel nanoparticles by atom transfer radical polymerization of *N*-isopropylacrylamide in aqueous media using PEG macro-initiator

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Abstract

PEG-*b*-PNIPAM block copolymers are synthesized by the atom transfer radical polymerization of NIPAM using PEG macro-initiator. When the polymerization temperature is 25 °C, the block copolymer is soluble in water, whereas the block copolymer is phase-separated to form micelles during polymerization as the polymerization temperature is raised to 50 °C, the temperature above the LCST of PEG-*b*-PNIPAM. To prepare stable hydrogel nanoparticles in water at room temperature, a small amount of *N*,*N*′-ethylenebisacrylamide is added as a cross-linker to the reaction system, where the size of nanoparticles is controlled by the composition of mixed solvent.

Keywords: Atom transfer radical polymerization; *N*-isopropylacrylamide; Nanoparticles

1. Introduction

Recently, stimuli-responsive hydrogel nanoparticles have attracted much attention, because they can respond quickly to their environmental stimuli in contrast to macroscopic gels [1]. Poly(*N*-isopropylacrylamide) (PNIPAM) is the most prominent temperature-responsive polymer because PNIPAM-based gels exhibit a sharp volume change at thier lower critical solution temperature (LCST) [2]. But, the synthesis of PNIPAM with controlled molecular weight with a narrow molecular weight distribution has not been satisfactory until recently. Only a few works on the living polymerization of *N*-isopropylacrylamide (NIPAM) have been reported by the reversible addition-fragmentation chain transfer (RAFT) [3–5] and the atom transfer radical polymerization (ATRP) [6].

The standard method used for preparation of polymeric particles is heterogeneous polymerization such as emulsion, dispersion, and suspension polymerization. Dispersion polymerization usually differs from suspension or emulsion polymerization in the initial state of polymerization system and the solubility of synthesized polymer, i.e., the monomer for dispersion polymerization is soluble in an organic solvent, which becomes nonsolvent for the resulting polymer [7–10].

In this paper, we report the dispersion polymerization of *N*-isopropylacrylamide (NIPAM) in aqueous media by ATRP using hydrophilic poly(ethylene glycol) methyl ether (PEG) as a macro-initiator in order to synthesize PEG-PNIPAM block copolymers. Although homopolymers of NIPAM by precipitation polymerization, block copolymers from PEG and PNIPAM (PEG-*b*-PNIPAM) by a ceric ion redox system, and their corresponding cross-linked micelles have been successfully prepared [11–15], the synthesis of PEG-*b*-PNIPAM by dispersion polymerization of NIPAM via ATRP and the preparation of hydrogel nanoparticle there from have not been reported yet to the best of our knowledge. The aim of this work is to prepare hydrogel nanoparticles by dispersion polymerization of NIPAM in aqueous media via ATRP and to control the size of nanoparticles by changing the reaction media.

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2. Experimental part

2.1. Materials

Poly(ethylene glycol) methyl ether ($M_n = 2000$ g mol^{-1}), copper(I) bromide (Cu^IBr), 2-bromoisobutyryl bromide, tris(2-aminoethyl)amine, triethylamine, and 4-(dimethylamino)pyridine were purchased from Aldrich Chemical Co. and were used as received, unless otherwise noted. Methylene chloride, diethyl ether, and tetrahydrofuran (THF) were purchased from Daejung Chemicals and Metals Co. *N*-Isopropylacrylamide and *N*,*N*′-ethylenebisacrylamide were purified by recrystallization from hexane. Tris(2-dimethylaminoethyl)amine (Me_6TREN) was synthesized by following the standard procedure [16]. PEG macroinitiator was synthesized by reacting poly(ethylene glycol) methyl ether with 2-bromoisobutyryl bromide [17].

2.2. Synthesis of PEG-b-PNIPAM

PEG-*b*-PNIPAM diblock copolymers were synthesized by ATRP of NIPAM in aqueous media at two different temperatures, 25 and 50 °C. First, PEG macro-initiator (0.1 mmol) and NIPAM (5.0 mmol) were charged into two flasks separately and then the flasks were evacuated and refilled with nitrogen repeatedly three times. Degassed water (10 mL) was added to each flask to prepare an initiator and a monomer solution. Cu^IBr (0.1 mmol) was placed into a new flask for polymerization, and then degassed water (20 mL) and Me_6TREN (0.1 mmol) were added into the flask under nitrogen atmosphere at 25 °C. After stirring the mixture for 5 min, the initiator and the monomer solutions, prepared in advance, were added to the polymerization flask and then the reaction mixture was allowed to polymerize at 25 °C for 24 h under stirring. Polymerization was quenched by adding a small amount of HCl(*aq*). The product was dialyzed with distilled water by using a dialysis membrane (CelluSep®, molecular weight cut-off = 3500) for 24 h in order to remove catalyst, ligand and unreacted monomer. After removal of water from the dialyzed solution, methanol was added to dissolve the product and then the solution was added dropwise into ether to precipitate. The precipitated product was filtered and dried in vacuum.

Hydrogel nanoparticles of PEG-*b*-PNIPAM were prepared by addition of *N*,*N*′-ethylenebisacrylamide (5 or 10 mol% of NIPAM) as a cross-linker in the monomer solution and then by following the same procedure described above at 50 °C in H_2O and H_2O/THF (1/1, vol/vol) mixture. After quenching the reaction with small amount of HCl(*aq*), the reaction mixture was dialyzed with distilled water by using the dialysis membrane for 7 days before measurement of dynamic light scattering and TEM.

2.3. Characterization

NMR measurement was performed with a 500 MHz spectrometer (Bruker, Advance 500 MHz) using D_2O as a solvent at room temperature. GPC analysis was performed using a Waters GPC 410 system with three Ultrahydrogel™ (120, 250, 500) after calibration with standard pullulan (Shodex standard p-82, SHOWA DENKO). Eluent of GPC measurements was distilled water/DMF (v/v = 9.5/0.5) containing NaOH 0.05 mol/L, and the flow rate was 0.6 mL/min. The cloud point of PEG-*b*-PNIPAM was determined by turbidity measurement using a Perkin–Elmer 8453A UV/visible spectrometer. The cloud point was defined as the temperature at the inflection point in the plot of the absorbance versus temperature, when the absorbance of polymer solution (0.1 wt%) was measured at 450 nm while the temperature was raised from 10 to 60 °C at an increment of 2 °C every 10 min. The size of micelle was determined by using a dynamic laser scattering spectrometer (Spectra Physics Model 127) and a detector (Brook Haven Instruments Co.). The scattered light of a vertically polarized He–Ne laser (633 nm) was measured at an angle of 90° at room temperature. The morphology of hydrogel nanoparticle was observed by using a transmission electron microscope (TEM, Philips CM).

3. Results and discussion

Synthetic procedures for preparation of hydrogel nanoparticles from PEG-*b*-PNIPAM synthesized by ATRP of NIPAM are represented in Fig. 1. When NIPAM is polymerized in water at 25 °C by ATRP, the polymerization is homogeneous because all the catalyst, ligand, initiator, monomer, and growing polymer chains are soluble in water. Very recently, it was reported that the ATRP of NIPAM in water was not successful, because a gel was formed immediately after the addition of catalyst [6]. On the contrary, gel was not formed in our system even for longer polymerization time of 24 h. This is probably because PEG block effectively prevents growing PNIPAM chains from formation of network due to physical crosslinking. GPC traces of PEG macro-initiator and synthesized PEG-*b*-PNIPAM are shown in Fig. 2(a) and (b), respectively, and polymerization condition, molecular weight and its distribution of PEG-*b*-PNIPAM are listed in Table 1. Monomodal and narrow molecular weight distribution indicates that PEG-*b*-PNIPAM is successfully synthesized by ATRP in water.

It is well-known that PNIPAM dissolves in water at room temperature but undergoes a phase separation when heated to higher temperature than 32 °C (LCST of PNIPAM). Since the cloud point of PEG-*b*-PNIPAM determined by turbidity measurement is 38 °C as shown in Fig. 3, the PEG-*b*-PNIPAM behaves as an amphiphilic diblock copolymer when the aqueous solution of PEG-*b*-PNIPAM was heated to a temperature higher than 38 °C, and thus forms micelles with hydrophobic PNIPAM chains as a core and hydrophilic PEG chains as a corona. When the micellar solution is

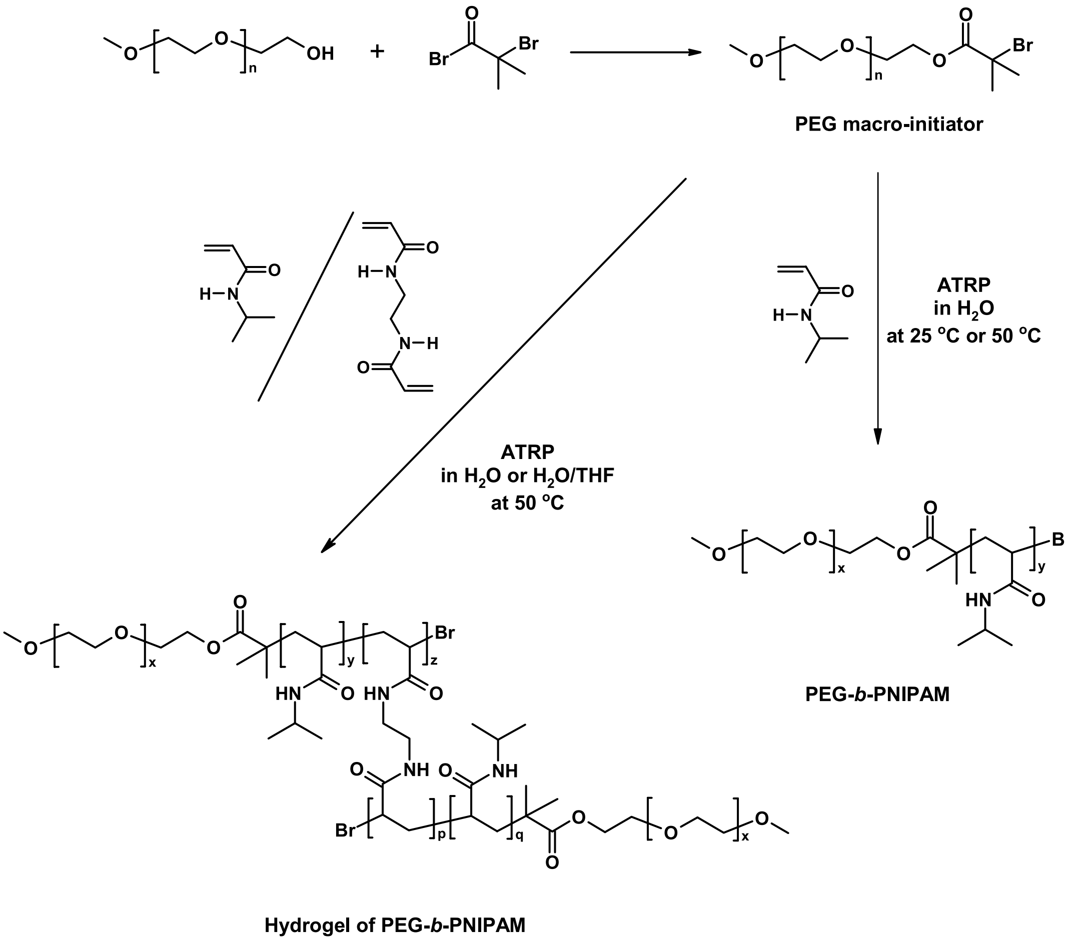

Fig. 1. Synthetic procedures for preparation of hydrogel nanoparticles of PEG-*b*-PNIPAM by ATRP in aqueous media.

cooled to room temperature, the micelle is broken to yield a clear solution, i.e., this temperature-responsive micellization is reversible.

When PEG-*b*-PNIPAM block copolymer is synthesized at 50 °C (above the LCST of PEG-*b*-PNIPAM), it is expected that micelles are formed during polymerization. Indeed, the color of reaction mixture changes from clear green to milky blue as is polymerized at 50 °C, indicating that micelles are formed in situ during polymerization. Similar behavior is observed in the case of anionic dispersion polymerization of styrene in hexane by using living poly(4-*tert*-butylstyrene) as a macro-initiator [7–10],

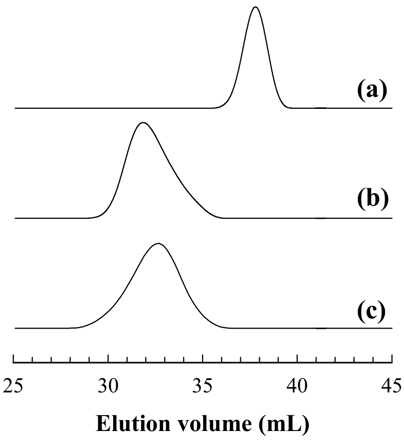

Fig. 2. GPC traces of polymers: (a) PEG macro-initiator, (b) PEG-*b*-PNIPAM copolymer synthesized at 25 °C in water, (c) PEG-*b*-PNIPAM copolymer synthesized at 50 °C in water.

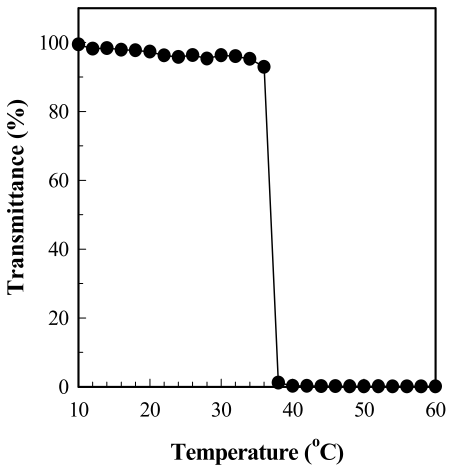

Fig. 3. Turbidity of PEG-*b*-PNIPAM in water as a function of temperature.

Table 1
Polymerization conditions and molecular weight and molecular weight distribution of PEG-*b*-PNIPAM

Solvent	Temperature (°C)	Cross-linker[a] (mol%)	M_n (g mol^{-1})		M_w/M_n[b]	Conversion (%)	Phase
			GPC	NMR[c]			
H_2O	25	–	7500	9800	1.45	>92	Homogeneous
H_2O	50	–	6600	7400	1.62	>63	Dispersion
H_2O	50	5	–	–	–	–	Dispersion
H_2O/THF[d]	50	5	–	–	–	–	Dispersion
H_2O	50	10	–	–	–	–	Dispersion

0.1 mmol of PEG macro-initiator, Cu^IBr and Me_6TREN with 5.0 mmol of NIPAM in 40 mL of solvent.

[a] *N,N′*-Ethylenebisacrylamide (5 or 10 mol% of NIPAM).

[b] Determined by GPC.

[c] Molecular weight of PNIPAM block was calculated from the ratio of the peak area of PEG block to that of PNIPAM block.

[d] H_2O/THF = 50/50 (vol/vol).

where living poly(4-*tert*-butylstyrene) acts as an initiator and at the same time forms a shell of micelle while polystyrene forms a core of micelle in hexane during polymerization.

Molecular weight distribution of PEG-*b*-PNIPAM synthesized at 50 °C is monomodal as shown in Fig. 2(c), but it is broader than that of PEG-*b*-PNIPAM copolymer synthesized at 25 °C. The GPC result also shows that the molecular weight of PEG-*b*-PNIPAM copolymer synthesized at 50 °C is lower than that of copolymer synthesized at 25 °C, as listed in Table 1. This is because the growing chain ends have low chance to react with monomers as the growing block copolymers form micelles. It is generally known that the heterogeneous nature of polymerization results in lowering the molecular weight of polymer.

To prepare stable hydrogel nanoparticles either in water or in water/THF at 25 °C, a small amount of *N,N′*-ethylenebisacrylamide (5 and 10 mol% of NIPAM) as a cross-linker is added to the monomer solution, followed by dispersion polymerization in water or in water/THF via ATRP at 50 °C, as shown in Fig. 1. When the size and its distribution of hydrogel nanoparticles are measured in water at 25 °C by dynamic light scattering, the average size of hydrogel nanoparticles prepared in H_2O and H_2O/THF are 67.5 and 503.3 nm, respectively, as shown in Fig. 4. This indicates that the use of mixed solvent of H_2O/THF increases the size of hydrogel nanoparticles. This is probably because THF increases the solubility of growing PNIPAM chains. This suggests that the size of micelle can be controlled by changing the composition of mixed solvent. A TEM image of hydrogel nanoparticles prepared at 50 °C in water with 10 mol% cross-linker shows that the hydrogel nanoparticles are stable at 25 °C and are spherical in shape, as shown in Fig. 5.

4. Conclusions

First, PEG-*b*-PNIPAM is synthesized by ATRP of NIPAM in water at 25 °C by using PEG macro-initiator. Since the cloud point of PEG-*b*-PNIPAM is 38 °C, the block copolymer solution is homogeneous during polymerization at 25 °C whereas the block copolymer is phase-separated to form nano-sized micelles at 50 °C. This temperature-responsive micellization is reversible. Second, when the block copolymer is synthesized under the same condition as

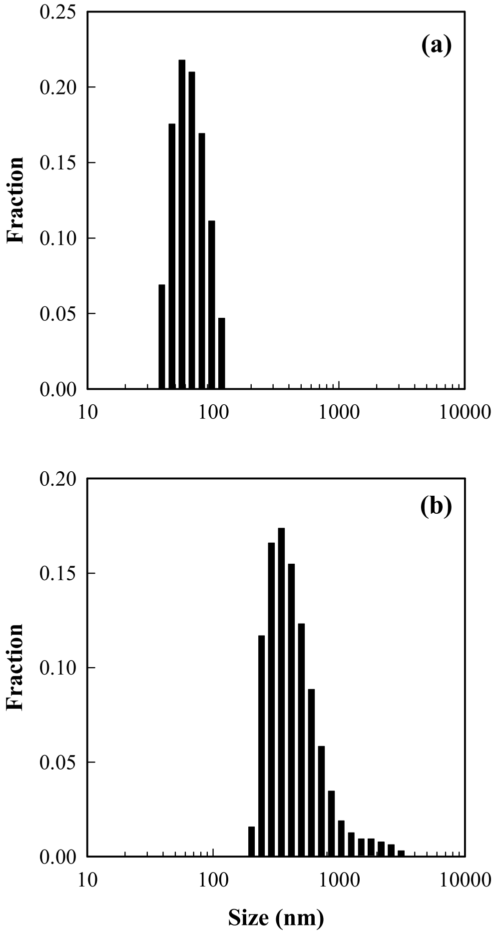

Fig. 4. Particle size distribution of PEG-*b*-PNIPAM hydrogel nanoparticles determined in H_2O at 25 °C: (a) copolymer synthesized in H_2O at 50 °C, (b) copolymer synthesized in H_2O/THF at 50 °C.

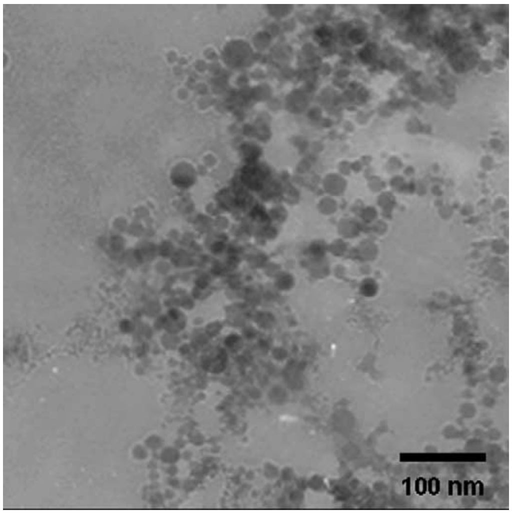

Fig. 5. TEM of hydrogel nanoparticles of cross-linked PEG-*b*-PNIPAM synthesized in H_2O at 50 °C.

above except the polymerization temperature, i.e., at 50 °C (above the LCST of PEG-*b*-PNIPAM) instead of 25 °C, micelles are formed in water during polymerization. Finally, when a small amount of *N*,*N'*-ethylenebisacrylamide is added as a cross-linker to prepare stable hydrogel nanoparticles at the lower temperature than its LCST, the hydrogel nanoparticles are stable at 25 °C and the size of resultant particles depends on the type of solvent, i.e., the use of mixed solvent increases the size of hydrogel nanoparticles.

Acknowledgements

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